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A new insulin-glucose metabolic model of type 1 diabetes mellitus: An in silico study

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ABSTRACT

Diabetes mellitus is a serious metabolic disease that threatens people's health. The artificial pancreas system (APS) has been generally considered as the ultimate cure of type 1 diabetes mellitus (T1DM). The simulation model of insulin-glucose metabolism is an essential part of an APS as it processes the measured glucose level and generates control signal to the insulin infusion system. This paper presents a new insulin-glucose metabolic model using model reduction methods applied to the popular but complex Cobelli's model. The performances of three different model reduction methods, namely Padé approximation, Routh approximation and system identification, are compared. The results of *in silico* simulation based on 30 virtual patients of three groups for adults, adolescents, and children show that the approximation error between this new model and the original Cobelli's model is so small that can be neglected. It can be concluded that the proposed simplified model can describe the insulin-glucose metabolism process rather accurately as well as can be easily implemented and integrated into an APS to make the APS technology more mature and closer to clinical use. The FPGA implementation, testing and further simplification possibility will be explored in the next stage of research.

1. Introduction

According to the statistical data from the World Health Organization (WHO), there are about 180 million diabetes patients all over the world and this figure is likely to be more than doubled by 2030 [1]. The deficiency of insulin secretion by β-cells is the main cause of type 1 diabetes mellitus (T1DM). Resulted from hyperglycemia and hypoglycemia, the complications of diabetes such as retinopathy, strokes, cardiovascular diseases, etc. can cause high rate of mortality [2]. The artificial pancreas system (APS) has been generally considered as the ultimate cure of type 1 diabetes mellitus, a form of diabetes mellitus that results from the autoimmune destruction of the insulin-producing beta cells in the pancreas. A typical APS contains three main parts: a continuous glucose measurement (CGM) system, a continuous subcutaneous insulin infusion (CSII) system, and a control algorithm based on an insulin-glucose metabolism model such as a model predictive control algorithm (MPC), etc. [3]. Unlike the recent successes in CGM and CSII development, the development of a reliable and general applicable insulin-glucose metabolic model is still far behind expectations [4–6].

Many different models which describe the metabolism process and kinetics of insulin and glucose have been proposed [1]. The Bergman model [7], which is also referred as a minimal

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model, is the most widely discussed model due to its simplicity because its model parameters are easy to identify. However, the main disadvantage of this model is also due to its simplicity because it was established based on several assumptions and the significant components of glucose-insulin interactions are neglected [8]. Based on the pathology of diabetes, Sorensen proposed a model with more than 20 differential equations determined by 44 parameters [9]. This model is not suitable for different subjects because all these parameters were obtained from literatures instead of being estimated from clinical data. Recently, Cobelli et al. [10] proposed a meal simulation model of glucose-insulin system based on a large amount of data collected from 204 normal subjects, the corresponding simulation environment has been approved by the Food and Drug Administration (FDA) as a possible substitute to animal trials [11]. This is a major improvement over previously proposed models due to the fact that it is based on a series of systematic clinical tests. However, the model consists of 12 nonlinear differential equations, 18 algebraic equations and 35 parameters [12,13]. Also, 31 parameters still need to be identified based on a series of experiment results. Hence this model is extremely difficult to be implemented into an implantable or wearable APS which is of a miniaturized size. Recently, there are a few new insulin-glucose metabolic systems have been proposed, in which the data-driven techniques such as neural network, fuzzy logic, etc. were employed [14–18]. However, those investigations mainly focused on the control algorithms development.

In order to reduce the complexity of the parameter identification task so that the model can be physically implemented and integrated into an APS, a simplified substitute of the FDA accepted Cobelli model by using transfer function strategy instead of differential equations is proposed in this paper. The model reduction methods are also applied to reduce the order of the system. In the following sections, the new insulin-glucose model of T1DM will be described at first, then the *in silico* simulation and results will be given in detail, finally the performance of the proposed model will be discussed and summarized.

2. Model reduction method

The approximation of a high-order system by a low-order model is of considerable importance in controller design and control system analysis. Generally speaking, a good model reduction method should satisfy several conditions. Firstly, the approximation error between the reduced model and the original model should be small enough to be ignored. Secondly, the reduced model must retain the stability of the original model. Thirdly, the computation process of the reduced model needs to be rapid and efficient.

Padé approximation method has been widely applied because of its computational simplicity and its excellent low-frequency approximation capability [19]. However, it has a serious disadvantage, *i.e.*, the obtained reduced model cannot retain the stability that the original model possesses. To overcome this problem, Hutton et al. [20] proposed Routh approximation method, which is one of the most attractive methods of model reduction because it retains the stability of the original system. In some additional cases, it is difficult to obtain the transfer function or state space model of the underlying system, then the system identification method is commonly used as a substitute method which only considers the input and output of the system. The main codes of Padé and Routh approximation method were listed in Appendixes B and C.

3. Insulin-glucose model of type 1 diabetes mellitus

As shown in Fig. 1, the insulin-glucose model of T1DM proposed by Cobelli et al. consists of 2 submodels: the insulin infusion submodel and the glucose submodel, which are linked by the control of insulin on endogenous glucose production and glucose utilization [21]. From the view of the glucose metabolism balance, two units which raise the concentration of plasma glucose are meal absorption from gut and endogenous glucose production. Meanwhile, two units which decrease the concentration of plasma glucose are glucose utilization and glucose renal excretion. Eq. (A1) in Appendix A is the differential equation of glucose submodel proposed by Cobelli et al. Other submodels and blocks will be discussed in detail in the following sections.

3.1. *Insulin infusion submodel*

As described by Cobelli et al., the differential equations of insulin infusion submodel (see Eq. (A2) in Appendix A, the parameter values can be found in literature [22]) contain 7 parameters which need to be estimated by parameter identification methods. By applying the Laplace transform to Eq. (A2) without considering the initial state of variables, the transfer

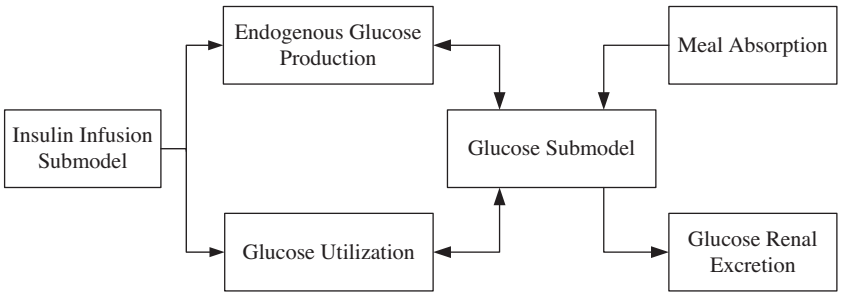

Fig. 1 – Cobelli's insulin-glucose model of T1DM [14].